

# 2011 Military Health System Conference

## Clinical and Rehabilitative Medicine Research Program Overview

*The Quadruple Aim: Working Together, Achieving Success*

COL Janet R. Harris RN PhD

26 January 2011



US Army Medical Research and  
Materiel Command

# USAMRMC

## *Mission and Vision*



## MISSION



**Responsively and responsibly create and deliver medical information and products for the warfighting family.**



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## VISION



**A trusted partner for leading biomedical research and materiel innovation for global health.**



## Customer-Focused Programs & Outcomes

**Fielded Medical Knowledge**

**CORE OUTCOMES**

**Fielded Medical Materiel**

Research to produce **medical knowledge**

**CORE PROGRAMS**

**Medical Research & Technology Program**

(1) Basic Research, (2) Applied Research, and (3) Advanced Technology Development to **prove tech-base concepts** for medical products (drugs, biologics & devices) and information

**Medical Advanced Development Program**

(4) Advanced Component Development & Prototypes and (5) System Development & Demonstration of tech-base concepts or commercial products into **FDA-approved war-ready medical products**

**Medical Strategic & Operational Logistics Program**

**Acquire, field, distribute, centrally manage, sustain/maintain and dispose of medical products, supplies and equipment** from the tech-base, advanced development, or from the commercial sources

**SPECIAL PROGRAMS**

**Congressional Special Interest Programs**

**SPECIAL OUTCOMES Targeted Outcomes**



# CHANGE DRIVERS FOR THE MILITARY MEDICAL RDA MISSION



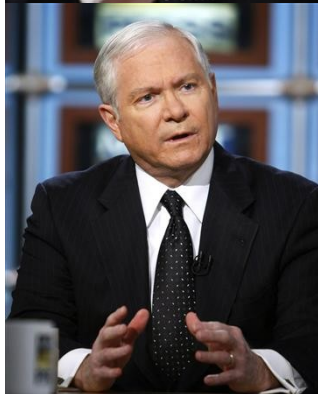
## Emphasis on Contemporary Health Threats and Joint

### *Secretary of Defense Guidance* Programs *Secretary of the Army Imperatives*



#### **June 26, 2008** **Secretary Gates** **Memorandum Caring for Our Wounded Personnel and Their Families**

"I request the development of a tailored plan to provide R&D investments that advance state of the art solutions for world class medical care with an emphasis on Post Traumatic Stress Disorder, Traumatic Brain Injury, prosthetics, Restoration Sight Eye-Care, and other conditions directly relevant to the injuries our soldiers are currently receiving on the battlefield."



#### **April 6, 2009** **Secretary Gates News** **Conference Details New** **Pentagon Priorities**

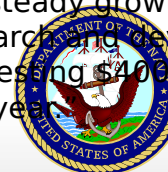
FY2010 Defense Budget: "Continue the steady growth in medical research and development by requesting \$400 million more than last year."

- SUSTAIN**
- ✚ Sustain Soldiers, Civilians and Families, through recruiting and improving quality of life
- ✚ Taking care of wounded Soldiers
- ✚ Rehabilitate Soldiers and get them back into the fight

- PREPARE**
- ✚ To continue to prepare Soldiers for success in the current conflict
- ✚ Continue to adapt its training and equipment to keep ahead of an adaptive enemy
- ✚ Training leaders and Soldiers

- RESET**
- ✚ Continue to reset units and to rebuild the readiness consumed in operations, to prepare them for deployments and future contingencies
- ✚ Reset for the future, not the past

- TRANSFORM**
- ✚ Transform the Army to meet the demands of the 21<sup>st</sup> century
- ✚ Continually modernize our forces and put our Cold War formations and systems behind us
- ✚ Future Combat Systems research and development is currently the Army's largest effort to modernize



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# CHANGE DRIVERS



*What is driving change in the military R&D environment?*

## Contemporary War Casualties

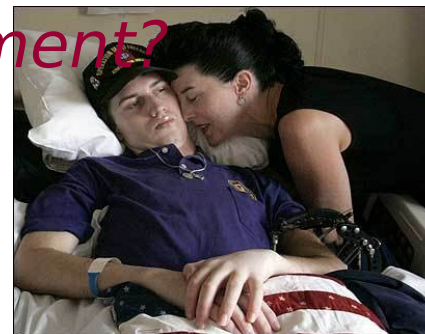
- Current war casualties are driving changes in healthcare needs and therefore changes in R&D
- Specific types of casualties driving changes:

### Traumatic Brain Injury (TBI)

	% Body Area	WWII	Korea	Vietnam	OIF/OEF
Head & Neck	12%	21%	21%	16%	29%
Chest	16%	14%	10%	13%	6%
Abdomen	11%	8%	8%	9%	11%
Extremities	61%	58%	60%	61%	54%

Owens, J Trauma FEB 2008

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TBI Suffered in Iraq



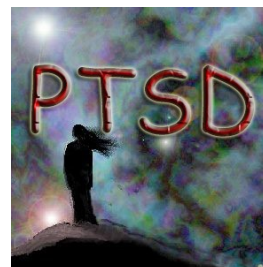
Trauma Team at Kirkuk Air Base in Iraq



Workshop at the Walter Reed Amputee Center



Blast Injury from Exploding Ordnance

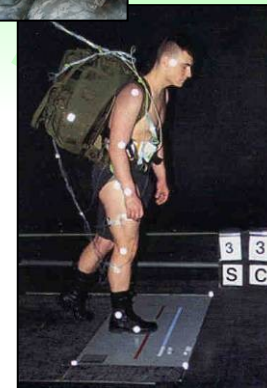


# RESETTING WOUNDED WARRIORS



## *R&D to Help Reset the Force*

Evidence-based  
return-to-duty  
standards and  
evaluation criteria

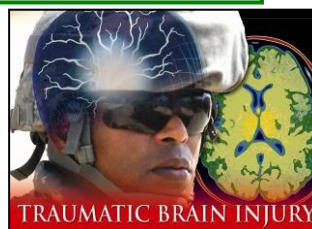


**Redeployment**

**Medical  
Evacuation**

**Reorientation  
and Reunion**

**Warrior Transition  
Units (Army)**  
**Transitional Reentry  
Sites** (Defense and Veterans  
Brain Injury Center (DVBIC))



**Return  
to Duty**

**Return  
to  
Civilian  
Life**





# CRMRP MISSION, FUNCTIONS, AND PARTNERS



## *Mission*

**Focus on definitive and rehabilitative care innovations required to reset our wounded warriors, both in terms of duty performance and quality of life**

## *Functions*

- Manage a core research program consisting of intramural and extramural efforts
- Leverage the congressional special interest research programs administered by USAMRMC, and research efforts in other federal laboratories, universities and industry.
- Coordinate the CRMRP research

Scientific Steering Committees, a Joint Program Committee, and a Joint Technology Coordinating Group were established to advise CRMRP on program direction and

priorities

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## *Coordinating Partners*



DoD laboratories and medical centers



DoD Congressional special interest programs



National Institutes of Health



Defense Advanced Research Projects Agency



Department of Veterans Affairs

# CRMRP PROGRAM AREAS



## Neuromusculoskeletal Injury: (Incl. Amputee)

- Address psycho-social recovery aspects
- Improve rehabilitation for limb salvage and spinal injury patients
- Exercise and fitness systems and strategies
- Improved orthotics, prosthetics, robotics to improve extremity function
- Incorporate neural interface/feedback



## Pain Management: (Acute/Chronic/Battlefield)

- Improve management of battlefield, acute and chronic pain
- Establish safety margins for individual prescriptions
- Identify and treat pain generators
- Develop strategies to empower patient in



## Regenerative Medicine and Transplants:

- Improve speed of healing and decrease scarring
- Regenerate missing tissue and repair gaps
- Improve functionality and appearance following craniofacial repair
- Develop architecture to integrate created tissue
- Reduce need for tissue rejection therapy
- Improve surgical approaches and limb/tissue function



## Sensory Systems: (Vision/Hearing/Balance)

- Repair damage to the eye and visual system
- Restore hearing
- Treat tinnitus
- Improve diagnostics
- Rehabilitate TBI-associated sensory dysfunction





# REHABILITATION



- Focuses on the rehabilitation of neuromusculoskeletal injuries, including amputee care and prosthetics
- Coordinating with the Center of Excellence for Extremity Injury and Amputation
- Major Initiatives:
  - Military Amputee Research Program
  - Prosthetics
  - Leveraging Orthopaedic Congressional funding (Peer-Reviewed Orthopaedic Research Program)
    - Major Extremity Trauma Research Consortium
    - Orthopaedic Rehabilitation Clinical Consortium



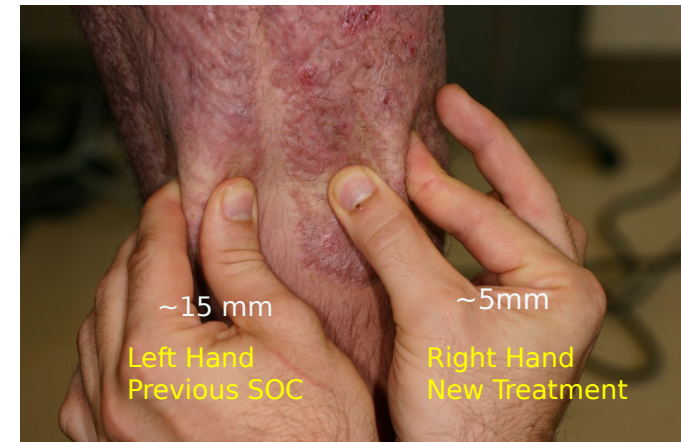
# Fraxellated CO2 Laser for Scar Contracture and Reduction



- **Problem**
  - Range of motion is reduced by burn scar contractures from thermal or chemical burns
- **Description**
  - Fraxellated laser: delivers independent, controlled patterns and depths of ablative and/or coagulative damage
  - Intent is to permit expansion of the skin and thereby reduce tension in scars

- **Studies**
  - Wilford Hall Medical Center
  - Initial studies conducted by Air Force
  - Study expansion being supported by DHP
  - Treatments were applied to burn scar contractures
    - ❖ Perioral and axillary regions
    - ❖ 5 treatments over 8-12 weeks
  - Assessed: range of motion, thickness, compliance and aesthetics (erythema and pigmentation)

- **Results:**
  - Immediate reduction in scar bulk
  - Smoothing of surface irregularities
  - Increased pliability
  - Pigmentation improvement
  - New production of scar collagen
  - Remodeling of scar



# REHABILITATION



## Investment Highlights

- **Military Amputee Research Program:** Congressional funding
  - Research embedded within military treatment facilities
  - Government, university and industry research
    - o Advanced prosthetics
    - o Rehabilitation
    - o Outcomes and program assessment
    - o Clinical management
    - o Database development/management

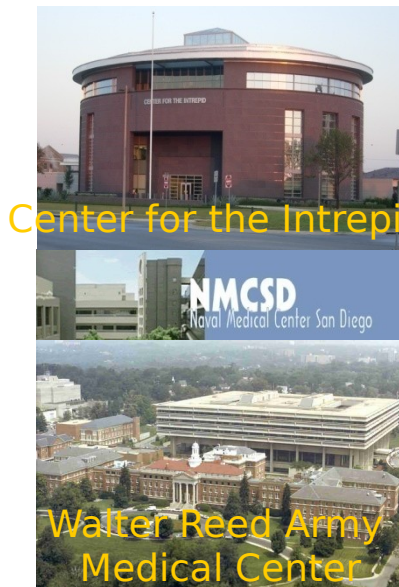
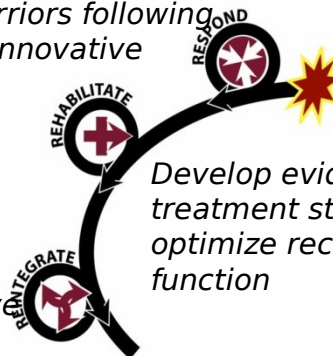


*Respond to the acute care needs of wounded warriors following injury through innovative solutions*

Post injury event

*Develop evidence-based treatment strategies to optimize recovery of function*

*Return to a full and productive life, to include return to duty, competitive sports, or a new vocation*





## Investment Highlights

### • Prosthetics:

- Lower Extremity: USAMRMC Managed Congressional funding
  - o C-Leg Generation 2 – Microprocessor powered knee (Commercialization NOV 2010)
  - o C-Leg Generation 3 – Ruggedized microprocessor controlled knee
  - o iWalk PowerFoot – Active plantar flexion push off
  
- Upper Extremity: VA-DARPA-USAMRMC Collaboration
  - o DEKA Arm – strap-and-go technology, foot-based control
  - o APL Arm – improved functionality, intended for targeted motor reinnervation
  - o Clinical trials for DEKA arm are planned to begin in Spring 2011, and APL arm studies are being developed



# REHABILITATION



## Coordinated Defense R&D - Prosthetics



- ✂ Revolutionizing Prosthetics Program
- ✂ Focused on upper extremity



- National Institute of Child Health and Human Development



White House Office  
of S&T Policy has  
requested a 10-year  
plan for prosthetics



- USAMRMC Clinical and Rehabilitative Medicine Research Program
- USAMRMC Telemedicine and Advanced Technology Research Center (TATRC) - Advanced Prosthetics and Human Performance Portfolio
- Military Amputee Research Program
- Transition partner for clinical trials – active duty population

- VA Prosthetics and Sensory Aids Service (PSAS)
- Prosthetics, orthotics, and assistive device research
- Transition partner for clinical trials – veteran population

# REHABILITATION



## The Major Extremity Trauma Research Consortium

- ✂ Johns Hopkins University led
- ✂ Consortium consists of orthopaedic researchers from U.S.
- ✂ Consortium aims include:
  - Improved outcomes and decreased fasciotomy in patients at risk for compartment syndrome by optimized clinical assessment, objective monitoring and tissue ultrafiltration
  - Outcomes following severe distal tibia, ankle and/or foot trauma: comparison of limb salvage versus trans-tibial amputation
  - Improving pain management in high energy orthopaedic trauma
  - Improving activity and quality of life following lower extremity trauma
- ✂ Funding amount to consortium: \$40 million (September 2010 – September 2015)





# REHABILITATION



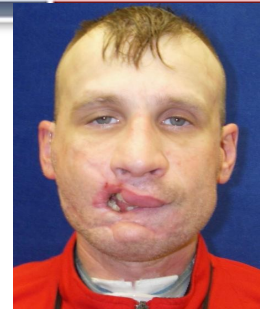
## Orthopaedic Rehabilitation Clinical Consortium

- ✂ Award pending
- ✂ University-led consortium will collaborate with the following MTFs:
  - San Antonio Military Medical Center (SAMMC)
  - Walter Reed National Military Medical Center (WRNMMC)
  - Naval Medical Center Portsmouth (NMCP)
  - Naval Medical Center San Diego (NMCSD)
- ✂ The goal of the Consortium is to improve rehabilitation of combat and combat-related neuromusculoskeletal injuries (including spine injuries, burns, and contractures, and excluding spinal cord injury [SCI])
- ✂ Funding amount for consortium: \$19.5 million over 5 years



## **Armed Forces Institute of Regenerative Medicine**

- ✂ Two consortia working together with the US Army Institute of Surgical Research (230 scientists)
  - Wake Forest - Pittsburgh University Consortium
  - Rutgers University - Cleveland Clinic Consortium
  - 28 Universities
  - 114 investigators - 30% of which are clinicians
  - 46 graduate students
  - 70 post-docs
- ✂ Total 5 yr funding of >\$270M
  - \$100M US Government funding from Army, Navy, Air Force, VA, and NIH
  - \$68M Matching funds from state governments and participating universities
  - \$109M in pre-existing research projects directly related to the deliverables of the AFIRM from NIH, DARPA, Congressional funding, NSF, philanthropy
  - DHP has supplemented \$19.8M for clinical trials since 2008



Cranio-Facial Reconstruction



Healing Without Scarring



Compartment Syndrome



Limb and Digit Salvage and Reconstruction



Burn Repair

# REGENERATIVE MEDICINE



## Investment Highlights

- **Clinical trials initiated in multiple areas:**

- Hand/face transplants with and without strategies for safer immunomodulation
- Engineered Skin Substitutes to treat >50% TBSA burns (both autologous and allogenic)
- Skin graft stretching to expand the size of autologous skin samples for grafting
- Autologous skin cell spraying to treat burn injuries with less scarring
- Bandage for Improved healing and scar reduction
- Autologous fat injections (alone and also enriched with stem cells) to reduce severity of burn scarring
- Use of porcine extracellular matrix to regenerate limb muscle form and function
- Segmental nerve gap regeneration using a novel nerve scaffold biomaterial





# PAIN MANAGEMENT



## Pain Management Task Force

- ✂ 2010 NDAA (Sec. 711) tasked the Secretary of Defense to develop and implement a comprehensive policy on pain management by the military health care system
- ✂ Army SG convened a multi-agency Task Force to define strategic needs for improving pain management, including research
- ✂ R&D recommendations
  - Develop collaborative pain research strategies that advance Warrior pain care and rapid translation
  - Validate pain research needs
  - Expand telemedicine capabilities to incorporate pain management initiatives
  - Improve military pain research strategic communications

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### TASK FORCE RECOMMENDATION

#### **A Standardized DoD and VHA Vision and Approach to Pain Management to Optimize the Care for Warriors and their Families**

<b>1</b>	Focus on the Warrior and Family - Sustaining the Force
<b>2</b>	Synchronize a Culture of Pain Awareness, Education, and Proactive Intervention (Medical Staff, Patients and Leaders)
<b>3</b>	Provide Tools and Infrastructure that Support and Encourage Practice and <b>Research Advancements in Pain Management</b>
<b>4</b>	Build a Full Spectrum of Best Practices for the Continuum of Acute and Chronic Pain, Based on a Foundation of Best Available Evidence

# PAIN MANAGEMENT



## Capability Gaps

- ✂ Acute and chronic pain management in the battlefield/remote locations and resource-limited environments
- ✂ Continuum of care from acute to chronic pain in a traditional environment
- ✂ Strategies to identify and treat pain generators
- ✂ Addressing psycho-social aspects of recovery (management of pain) - knowledge and treatment strategies / therapies for treating pain and co morbidities

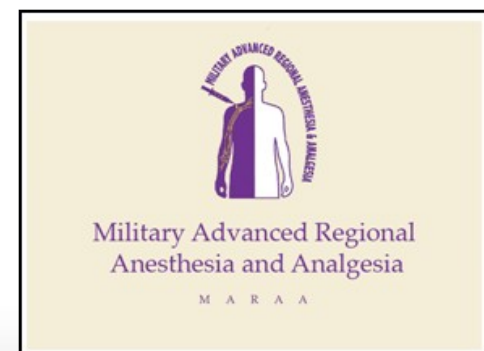


# PAIN MANAGEMENT



## Regional Anesthesia and Pain Management Initiative

- Defense and Veterans Pain Management Initiative (DVPMI)
  - Conducts acute and chronic pain research
  - Capabilities for consultation, referral, policy development, publications, education and training
- Research
  - Regional anesthesia - validation conducted in deployed set
  - Translational research - biological effects of regional anesth
  - Biomarkers for pain
  - Outcomes evaluation (RAMPOS, POWER)
  - Evidence based practice
- Funding
  - Established by CSI funding
  - Transitioning to DHP
- Value to the Warfighter
  - First ever deployed Acute Pain Service with British Coalition Forces, Camp Bastion, Afghanistan
  - SME to OTSG on Pain Task Force - driving force behind all pain initiatives
  - First research since WWII on pain immediately following wounding
  - Since 2003 all advancements in battlefield pain control from point of injury, through air evacuation, to CONUS have been a direct result of the DVPMI
  - 2009: Military Advanced Regional Anesthesia & Analgesia (MARAA)





# Molecular Signatures of Chronic Pain Subtypes

Rehabilitation – Acute and Chronic Pain Management



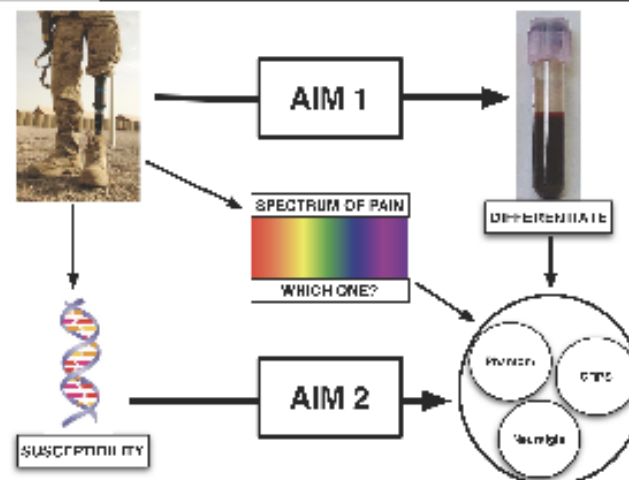
DMRDP

PI: Andrew Shaw MD

Org: Duke University Medical Center

## Problem, Hypothesis and Military Relevance

- **Problem:** (1) There are no good tests to differentiate between different types of chronic amputation pain. (2) There are no good ways to measure susceptibility to chronic pain subtypes (phantom limb pain, neuralgia, CRPS).
- **Hypothesis:** (1) Plasma protein signatures can identify each type of amputation pain. (2) Sequencing the genes of these proteins can identify patients at risk for each type of pain.
- **Military Relevance:** New, objective tools facilitating the differential diagnosis and risk assessment of chronic pain states would allow more focused deployment of rehabilitation resources, and thus permit earlier return to functional status for injured warriors.



## Proposed Solution

- **Aim 1a:** Describe the molecular (proteomic) signatures of phantom pain, neuralgia pain and Complex Regional Pain Syndrome (CRPS) in 450 war injured amputees.
- **Aim 1b:** Describe the biology of chronic amputation pain subtypes in terms of the peptides and proteins expressed in early and late blood samples from amputees
- **Aim 2a:** Generate list of candidate risk genes for each subtype of amputation pain.
- **Aim 2b:** Sequence genes of proteins from Aim 2a to find new polymorphisms associated with functional differences and risk of each pain subtype.

## Timeline and Direct Cost

Activities	Year 1	Year 2	Year 3
Compliance and approval	■		
Recruit subjects		■	
Discovery Proteomics (Aim 1)		■	
Gene Sequencing (Aim 2)		■	
Validation studies (Aims 1 & 2)			■
Report preparation		■	■
Estimated Budget (\$K)	400K	400K	200K

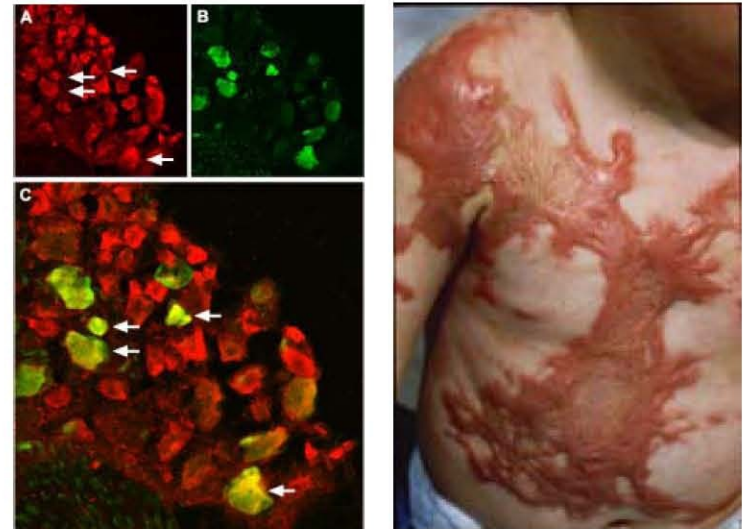
# Role of endogenous agonist of TRPV1 in burn pain

PI: Laura McGhee

Org: US Army Institute of Surgical Research

## Problem, Hypothesis and Military Relevance

- Problem: Management of acute pain after burn injury to prevent development of chronic pain
- Hypothesis: Burned skin releases oxidized linoleic acid metabolites (OLAMs) that function as endogenous TRPV1 agonist. Potential analgesics may be developed from compounds that block OLAM synthesis or action.
- Military Relevance: Since the beginning of OIF/OEF, the US Army Institute of Surgical Research has cared for over 800 soldiers injured in the conflict. Their pain management is often complex and difficult. Often the soldiers are on large amounts of opioids to manage their pain and still report high levels of pain.



## Proposed Solution

- Specific Aim 1: Evaluate the analgesic efficacy of NDGA and anti-OLAM antibodies in a rat model of burn pain. This injury produces a third degree burn with thermal hyperalgesia that is still significant at 14 days after injury. The pharmacological studies will evaluate 3 P450 inhibitors and 3 combinations of anti-OLAM antibodies as compared to vehicle controls.
- Specific Aim 2: Evaluate the correlation between clinical scar tissue levels of OLAMs and patient reports of pain intensity using a 100mm VAS. Discarded burn tissue will be collected from the USAISR during OR procedures. The tissue will be assayed for OLAMs using immunoassay methods. Pain levels will be correlated to OLAM levels.

## Timeline and Cost

Activities	FY	10	11	12
Evaluate the analgesic efficacy of OLAM synthesis inhibitors				
Evaluate the analgesic efficacy of anti-OLAM antibodies				
Collect scar tissue and assay for OLAM levels. Correlate OLAM levels and pain levels				
Estimated Budget (\$K)		250K	250K	250K

# Exploration of a novel persistent reversal of pathological pain: mechanisms and mediators

Rehabilitation: Acute and Chronic Pain Management

PI: Watkins, Linda R.

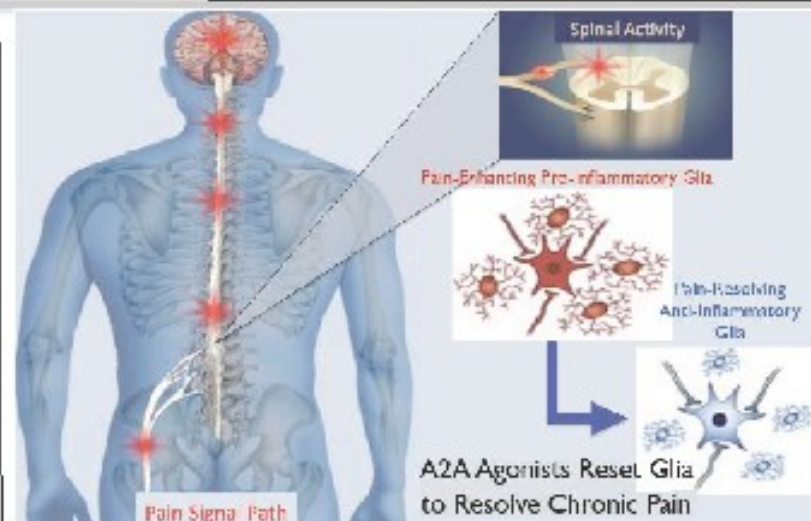
Org: University of Colorado at Boulder



DMRDP

## Problem, Hypothesis and Military Relevance

- Due to the physical nature of their work, military personnel often suffer from nerve injury leading to chronic pain.
- Chronic pain is poorly managed by currently available therapeutics, which target neurons of the pain pathway.
- We believe that glial cells, immune-like cells in the spinal cord, are the true mediators of chronic pain.
- We have discovered a novel non-opioid, non-addictive therapeutic (Adenosine 2A [ $A_{2A}$ ] agonists) which targets glia.
- $A_{2A}$  agonists resolved pathological pain in an animal model for 4+ weeks after a single intrathecal injection, an unprecedented result of great promise.
- **Hypothesis:** Shifting spinal cord glia to a pain-resolving anti-inflammatory state using  $A_{2A}$  agonists could resolve chronic pain.



## Proposed Solution

- The proposed project explores basic science issues, ranging from behavioral studies to characterize the phenomenon to mechanistic studies to understand the unprecedented, enduring pain resolution induced by intrathecal  $A_{2A}$  agonists.
- Aim I tests  $A_{2A}$  agonist utility for: (a) treating long-standing neuropathic pain (chronic constriction injury; CCI), (b) treating neuropathic pain in other DoD relevant models (Chung, spinal cord injury), & (c) providing continuing pain resolution with repeated dosing over time (CCI).
- Aim II explores mechanisms underlying  $A_{2A}$  resolution of CCI-induced neuropathic pain by testing if pain resolution: (a) is due to  $A_{2A}$ -induced IL-10, (b) acts via protein kinase A or C, (c) acts by resetting glia into an alternatively activated state, or (d) is unique to the  $A_{2A}$  adenosine receptor subtype.

## Timeline and Direct Cost

Activities	FY	10	11	12
Characterization Studies (Specific Aims IA, IB, & IC): efficacy if chronic pain; generalization to other pathological pain models of DoD relevance; efficacy with repeated treatment;				
Mechanistic Studies (Specific Aims IIA, IIB): role of IL-10 early & late; intracellular signaling pathways				
Mechanistic Studies (Specific Aims IIC, IID): glial alternative activation; adenosine receptor subtypes				
Estimated Budget (\$K)		333.3	333.3	333.3



## Capability Gaps

- Inadequate treatment of traumatic injuries, war-related injuries, and diseases to ocular structures, and the visual, vestibular or hearing system(s)
- Prevention, treatment, and mitigation of sensory dysfunction associated with traumatic brain injury (TBI) and war-related injuries
- Inadequate vision restoration
- Inadequate hearing restoration
- Population-based studies, epidemiology
- Inadequate ocular diagnostics
- Inadequate prevention strategies
- Inadequate rehabilitation strategies





# SENSORY SYSTEMS



## Investment Highlights

- New start program area in 2010
- Focused on restoration and rehabilitation of traumatic injury
- Coordinating with the Vision and Hearing Centers of Excellence
- Vision
  - Corneal wound repair
  - Novel therapeutics, including regenerative medicine
  - Rehabilitation of TBI-related visual dysfunction
- Hearing and Balance
  - Hearing restoration
  - Treatment of tinnitus
  - Rehabilitation of balance disorders

# Preserving Vision After Traumatic Brain Injury

Diagnosis and Treatment of Brain Injury; Polytrauma and Blast Injury/Treatment of Sensory System  
Traumatic Injury (Vision, Hearing, and Balance)

PI: Johnny Tang, M.D.

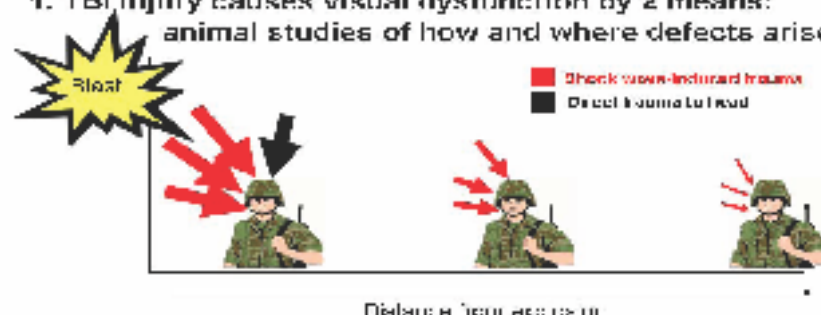
Org: University Hospitals Case Medical Center



## Problem, Hypothesis and Military Relevance

- Traumatic brain injury (TBI) in military and civilian situations commonly results in significant vision loss or dysfunction, and this abnormality remains unexplained and untreatable.
- Our goal is to develop an animal model that reproduces the effects of TBI from munitions and improvised explosive devices (IEDs) and to develop therapies to inhibit damage from TBI.
- This work responds to needs in the FY10 DMRDP program, with particular focus on diagnosis and treatment of traumatic brain injury, and polytrauma and blast injury.

1. TBI injury causes visual dysfunction by 2 means:  
animal studies of how and where defects arise



2. Development of therapies to inhibit TBI-induced visual dysfunction:  
PARP inhibitor  
iNOS inhibitor  
local hypothermia

## Proposed Solution

- We will create an animal model of TBI secondary to shockwave and blunt trauma to (1) investigate and characterize the functional and structural abnormalities that develop in the visual axis, (2) investigate where in the visual system the trauma-induced defects develop using a new and advanced functional imaging method (manganese-enhanced magnetic resonance imaging (MEMRI)), and (3) treat TBI pharmacologically using inhibitors of poly(ADP-ribose) polymerase (PARP), inducible isoform of nitric oxide synthase (iNOS), and local hypothermia.
- We have significant preliminary data that indicates the imminent feasibility in our plan.

## Timeline and Direct Cost

Activities	FY	10	11	12
Development and Characterization of an animal model of TBI using fluidic percussion and shockwave injury.				
Identification of pathways/mechanisms using biochemical, electrophysiology and advanced neuroimaging studies.				
Development of treatment modalities for TBI/TON.				
Estimated Budget (\$K)		\$240	\$250	\$260

# Photoreceptor loss stimulates retinal plasticity that causes visual dysfunction.

## Polytrauma and Blast Injury: Treatment of Sensory System Traumatic Injury (Vision, Hearing, and Balance)

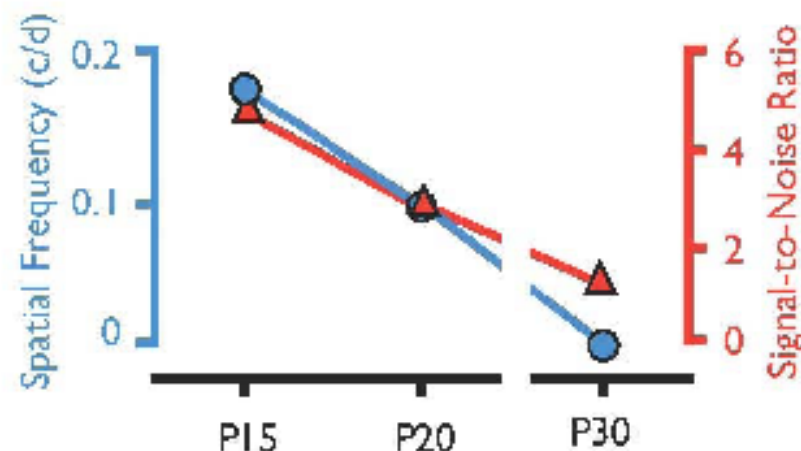


PI: Dr. Glen Prusky

Org: Weill Cornell/ Burke Medical Research Institute

### Problem, Hypothesis and Military Relevance

Retinal damage, including photoreceptor degeneration, is a common consequence of military action. Accumulating evidence suggests that such damage stimulates retinal plasticity that leads to maladaptive reorganization of surviving retinal circuits. Blocking such maladaptive changes would provide a novel target to maintain visual function following retinal damage, and reversing maladaptive retinal physiology could be an important route to stimulate recovery of visual function. Understanding the causal relationship between photoreceptor integrity, retinal physiology and visual function is the first step in identifying and targeting these processes. We hypothesize that the successful treatment of visual dysfunction resulting from retinal damage will depend ultimately on retinal interventions that stimulate or maintain retinal output that normally functions to maintain visual 'signals' above physiological 'noise'. To this end, we will investigate a causal role for retinal output in predicting visual function by quantifying visual behavior, photoreceptor integrity, and retinal ganglion cell (RGC) output, in animal models in which loss of visual function (experimental 'necessity'), and preservation of visual function (experimental 'sufficiency'), are independently assessed.



### Proposed Solution

First, the spatial frequency threshold and contrast sensitivity of optokinetic tracking will be assessed in a given animal (~30 minutes). Animals will then be anesthetized and the physiological output of the retina will be evaluated with *in vivo* extracellular recordings of single RGCs - the output cells of the retina. Following this, the retina from one eye will be removed for slice electrophysiological assessment of synaptic components. Finally, the other eye will be excised and prepared for anatomical assessment. The results from each of these stages will be collated and group differences between degenerating animals, and non-degenerating, age-matched control animals will be quantified.

### Timeline and Direct Cost

Activities	10	11	12
Salaries, maintenance of equipment, animal costs, "necessity" experiments	\$300,000		
Salaries, maintenance of equipment, animal costs, "sufficiency" experiments		\$300,000	
Salaries, maintenance of equipment, animal costs, anatomical experiments			\$300,000
Estimated Budget (\$K)	300,000	300,000	300,000

# Restoring vision after optic nerve injury

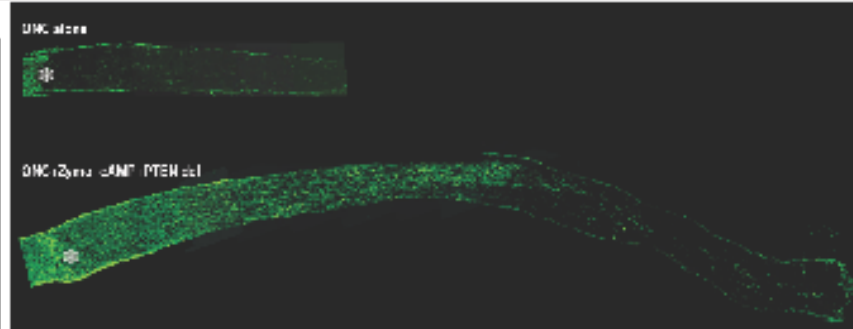
Polytrauma and Blast Injury: Treatment of Sensory System Traumatic Injury (Vision, Hearing, and Balance)

PI: Larry Benowitz, PhD Org: Children's Hospital Boston and Harvard Medical School



## Problem, Hypothesis and Military Relevance

- The optic nerve does not regenerate if injured, leaving victims of traumatic nerve damage with lifelong losses in vision
- Regenerative failure is associated with the death of projection neurons (retinal ganglion cells, RGCs), an inability of RGCs to extend axons, and inhibitory signals in the extracellular environment
- Research is aimed at protecting RGCs from death, enabling these cells to regenerate axons to their central target areas, and restoring vision.
- Research addresses the Project and Task of Blast Injury and Protection/Restoration of sensory functions. May also be applicable to other instances of CNS injury, such as TBI.



Longitudinal sections through mouse optic nerves 2 weeks after optic nerve crush (injury site shown with asterisks on left). Regenerating fibers are visualized with antibodies to GAP-43. *Top*: Untreated mouse shows no regeneration. *Bottom*: Mouse treated with intraocular Zymosan, elevation of cyclic AMP, and deletion of the PTEN gene shows extensive regeneration.

## Proposed Solution

- Investigate the mechanisms that underlie RGC death after nerve damage
- Develop strategies to promote RGC survival
- Continue developing strategies to enable RGCs to regenerate axons to their central target areas
- Combine the above approaches to maximize optic nerve regeneration
- Determine whether optic nerve regeneration restores visual functioning.

## Timeline and Direct Cost

Activities	10	11	12
Identify causes of RGC death after axotomy. Develop strategies to prevent cell death.			
Investigate combinatorial treatments to maximize RGC survival and promote axon regeneration.			
Investigate above treatments result in functional recovery. Write paper(s).			
Estimated Budget (\$K)	204,011	206,536	209,137



# Rehabilitation of Visual and Perceptual Dysfunction after Severe Traumatic Brain Injury



PI: Eliezer Peli

Org: Schepens Eye Research Institute, Harvard Med. School

## Problem, Hypothesis and Military Relevance

- **Problem:** Severe TBI causes homonymous hemianopia and spatial neglect which impair detection of obstacles on the affected side, resulting in unsafe walking and driving. Peripheral prism (p-prism) glasses, an optical treatment we have developed, has shown great promise for hemianopia. Objects from the blind side appear to be on the seeing side, which can be helpful, but can also be confusing.
- **Hypothesis:** Perceptual-motor training will facilitate adaptation and correct perceived direction of obstacles when using p-prism glasses, resulting in improved mobility.
- **Military Relevance:** We address the Vision component of the *Restoration and Rehabilitation of Sensory System Traumatic* task in the *Rehabilitation* project.



Peripheral prism (p-prism) glasses on right spectacle lens of a right hemianope. The glasses provide visual field expansion (up to 30°) on the blind side, which is helpful for obstacle avoidance when walking

## Proposed Solution

- Extend our research to determine whether p-prism glasses improve function in TBI patients with neglect;
- Evaluate whether perceptual-motor training aids perceived direction adaptation when using p-prism glasses in TBI patients with hemianopia with and without neglect;
- Evaluate whether the training transfers and improves performance on other more "real world" tasks (collision judgments while walking in a virtual mall, and detections while driving in a simulator);
- Determine whether p-prism glasses are more effective than other treatments for hemianopia and neglect

## Timeline and Cost

Activities	FY	10	11	12
Final development of the training tool and details of the training regimens		■		
Evaluations of improvements in function, direction adaptation and transfer to real-world tasks		■	■	
Evaluate whether p-prism glasses are more effective than other treatments			■	■
Estimated Total Budget (\$K)		\$675K	\$601K	\$696K

# Wearable Visual Aid as Treatment for TBI Associated Visual Dysfunction



**Product Status:** FY09 VRP Awarded 16 SEP 10

**USAMRMC Portfolio:** Vision

**Principal Investigator:** James Weiland, PhD

## Capability / Product Description

- Develop a simultaneous localization and mapping (SLAM) algorithm for use in multiple object detection and identification to assist in ambulation and navigation.
- Develop neurally inspired attention algorithms that detect important objects in an environment to assist in search tasks.
- Develop an algorithm for determining the gist of the user's environment to assist in the selection of the most suitable task-specific algorithmic aid.
- Implement a prototype wide-field, wide-dynamic-range camera for image capture and integrate it into a wearable system with a patient cueing interface, and test the portable system on visually impaired volunteers in real-world situations.

## Clinical Development & Acquisition Phases

- Currently at PR 4

## Funding

	<b>FY09</b>	<b>FY10</b>	<b>FY11</b>	<b>FY12</b>	<b>FY13</b>	<b>FY14</b>	<b>FY15</b>	<b>FY16</b>	<b>FY17</b>
<b>Funded</b>	\$1,997,191								

## Development Organizations

- University of Southern California

## Benefits / ROI

This project addresses important issues of algorithm development and hardware implementation that have both specific and broad impact (i.e., individuals suffering from vision loss )

The completion of the study has a reasonable likelihood of leading to important advances and impacting patient care in the short term.

## Key Risk(s) / Mitigation Strategy

- Possible lack of commercial interest



# Visual Information Restoration and Rehabilitation via Sensory Substitution Technology

**PI:** Dr. Aimee Arnoldussen

**Org:** Wicab, Inc.



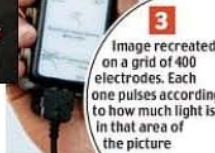
## Problem, Hypothesis and Military Relevance

- **Problem:** There is a need for new technologies for blinded service men and women that enhance safety, mobility and independence
- **Hypothesis:** The BrainPort vision device will improve activities of daily living, quality of life and rehabilitation for the blind
- **Military Relevance:** The BrainPort vision device is the only new technology likely available in the near term to address safety and mobility issues resulting from blinding injuries sustained in recent military conflicts. The military has historically been the leader in developing prosthetic devices.

## Proposed Solution

- The BrainPort vision device is a visual prosthetic that enables perception of visual information using the tongue and camera system as a paired substitute for the eye
- Visual information is collected from a video camera and translated into gentle electrical stimulation patterns on the surface of the tongue
- With training users perceive shape, size, location and motion of objects in their environment
- The BrainPort vision device is immediately available for evaluation by wounded warriors and veterans

## HOW THE DEVICE WORKS



**1** Inch-long camera hidden in sunglasses sends image to a handheld control unit







**2** The control unit converts the image into a low resolution black, white and grey picture

**3** Image recreated as a grid of 400 nodes. Each node calculates how much light is coming from that area of the picture.

**5** Brain eventually learns to 'see' the shape detected on tongue

**4** User 'feels' the shape and detects movement on their tongue

## Timeline and Cost

Activities	FY	10	11	12
BrainPort iterative user testing				
Software enhancement development				
Implementing hardware and software improvements				
Estimated Budget (\$2,241K)		748K	745K	748K

# SUMMARY



- CRMRP is DoD's research program focused on resetting wounded warriors
- Collaboratively working with other government agencies
- Activities underway to develop the 10-year plan for prosthetics
- Leveraging of Congressional funding has significantly advanced the programs, especially prosthetics and rehabilitative medicine
- CRMRP is managing challenges; although policy drivers may be needed to realize full potential of these technologies



# CRMRP POINTS OF CONTACT



## **COL Janet Harris**

Director  
301-619-8836  
[janet.harris@us.army.mil](mailto:janet.harris@us.army.mil)

## **MAJ Regina Davey**

Interim Deputy Director  
301-619-7255  
[regina.davey@us.army.mil](mailto:regina.davey@us.army.mil)

## **Dr. Brian Pfister**

Strategic Portfolio Manager, Regenerative  
Medicine  
301-619-8836  
[Brian.pfister@us.army.mil](mailto:Brian.pfister@us.army.mil)

## **Dr. Dettrick Stith**

Strategic Portfolio Manager,  
Neuromusculoskeletal Rehabilitation  
301-619-9811  
[Dettrick.stith@us.army.mil](mailto:Dettrick.stith@us.army.mil)

## **Dr. Tony Gover**

Strategic Portfolio Manager, Pain Management  
Strategic Portfolio Manager, Vision Restoration  
301-619-9560  
[Tony.d.gover@us.army.mil](mailto:Tony.d.gover@us.army.mil)

## **Mr. Joel Glover**

Strategic Portfolio Manager, Hearing  
Restoration and Rehabilitation  
301-619-8836  
[Joel.glover@us.army.mil](mailto:Joel.glover@us.army.mil)

## **Ms. Nancy Lingman**

Strategic Portfolio Manager, Cognitive  
Rehabilitation  
301-619-9430  
[Nancy.lingman@us.army.mil](mailto:Nancy.lingman@us.army.mil)

## **Mr. Christian Walker**

Commercialization Manager  
301-619-8932  
[Christian.walker@us.army.mil](mailto:Christian.walker@us.army.mil)

## A collage of images related to the Iraq War. The top left shows soldiers in camouflage uniforms standing in a desert environment. The top center shows a soldier in a white uniform with an American flag patch on the sleeve, looking down. The top right shows the American flag waving against a sunset background. The center features a large oval inset showing a close-up of hands holding a small American flag. The bottom left shows a long row of American flags laid out on the ground. The bottom center shows a medical scene with a soldier lying on a stretcher being attended to by medical personnel. The bottom right shows a soldier in camouflage uniform covering his face with his hands, appearing distressed. In the bottom left corner, there are two circular logos: the Department of the Army seal and the United States Army Medical Department seal.

